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Problems Requiring Solution Through Field Studies

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Available epidemiologic and other indirect evidence strongly supports the assumptions (a) that leprosy is an infection caused by *M. leprae,* (b) that the sources are exclusively human cases discharging bacilli, (c) that transmission is by direct or indirect contact through the skin, and (d) that reactivity to lepromin is positively associated with resistance.

Cultivation and transmission experiments must certainly come first and a continued search must be made for better drugs in the treatment of the disease. There are many puzzling and unexplained features of leprosy, however, which can be answered only by more field studies. The following deserve consideration:

POSSIBLE SOURCES OF INFECTION

Evidence points strongly to "open" cases, not always of the lepromatous type. Hanks [14] and Shepard [23] have shown that lepromatous cases harbor and may discharge enormous numbers of bacilli from ulcerated skin and nasal lesions. Bacilli might even escape from unbroken skin lesions through desquamating epithelium, as reported by Muir [18] and Weiner [26]. It is common knowledge that when contact with a previous case can be established, it is traceable far more frequently to lepromatous than to tuberculoid cases. The Cebu studies of the Leonard Wood Memorial [8 13] showed the attack rate for household contacts of lepromatous cases to be four times higher than for contacts of tuberculoid cases and at least six times higher than among noncontacts, while the attack rate among contacts of tuberculoid cases was at most less than twice that for unexposed persons.

It is well known that an appreciable proportion of all tuberculoid cases become bacteriologically positive during periods of exacerbation or reaction. The continued maintenance of high prevalence levels in endemic areas where the tuberculoid type constitutes 90 per cent or more of all leprosy cases might be attributed in part to the unknown proportion becoming reactional and "open" at some time. To assess the role of the tuberculoid form further in the spread of the disease, comparative studies should be made in different geographic areas of the relative frequency of the occurrence of such reactional episodes.

Exposure to previously known cases cannot be established in a large proportion of all leprosy infections. The long incubation period may account in part for this failure. If known cases constituted the sole source of leprosy, a conscientious investigation of the disease in young children should disclose positive contact in most, if not all instances. Such a finding has never quite materialized. Of 19 new cases in children under 5 years of age in Cebu [13], we were unable to establish exposure to a known leprosy case in 10 or 52.6 per cent of the children. "Missed" cases with very inconspicuous lesions could account for some of the infections, and a search for such cases should always be made.

The existence of symptomless but infectious cases of leprosy is frequently suspected and could be a plausible explanation for otherwise untraceable infections. Evidence of subclinical leprosy was first advanced by Figueredo and Desai [9], who found acid-fast bacilli in the skin of a large proportion of apparently healthy and lepromin-positive contacts, and only in a much lower proportion of noncontacts. Desai [4] subsequently reported finding acid-fast bacilli in no less than 610 or 32.9 percent of 1,852 contacts. Dharmendra [5] also found small numbers of acid-fast bacilli in the skin of symptomless persons, although in a far lower proportion than that claimed by Desai. He strongly counsels against con-

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sidering these as instances of subclinical leprosy, because of the strong possibility that the bacilli could be merely saprophytes.

The existence of asymptomatic leprosy infections must be verified by more field studies, which should also include one of their relative frequency in contacts and noncontacts. Desai's apparent finding that they are significantly more frequent among contacts would be expected if these were actually instances of subclinical leprosy. Shepard's method of inoculation into mouse foot pads ([24]), which has been verified by others, might be used as a possible means of identifying the bacilli as *M. leprae*. A "lepromin" prepared from Shepard's infected mouse foot pads gave negative Mitsuda reactions in lepromatous patients and positive ones in tuberculoid patients, i.e., reactions that were almost identical with those to regular lepromin ([25]).

MODE OF TRANSMISSION

Leprosy is assumed to be transmitted by direct skin to skin contact or by indirect contact through contaminated objects. The possibility should be considered of transmission by biting or blood-sucking insects of limited or domestic range of movement, such as bedbugs, fleas and lice, which have a widespread distribution in areas where leprosy is highly endemic. The usual inability of the disease to spread after being introduced into nonendemic areas might be attributed in part to the absence of possible arthropod vectors. Acid-fast bacilli have been found in many insects, but there is no procedure as yet for their definite identification as *M. leprae*. Inoculation into mouse foot pads is suggested. Combined field and laboratory studies are naturally required to verify possible arthropod transmission in leprosy. On the epidemiologic side, studies should be made to determine if bedbugs, fleas, or lice are significantly more frequent in households where new cases occur than in others. Flying insects of wide range are unlikely to be involved in the spread of a disease so focal in its distribution as leprosy.

PORTAL OF ENTRY

M. leprae are assumed to enter through wounds and other breaches in skin continuity, especially in skin diseases, which are very common in children of endemic areas. If the point of entry is the skin, it is obvious that a break in continuity would be a strong predisposing factor. Marchoux ([17]) reported a case of leprosy in a medical attendant in France who was pricked with a needle during an operation for removal of a leprous nodule; nine years later he developed a bacteriologically positive and anesthetic lesion around the site of the puncture in the hand. Porritt and Olsen ([21]) have reported the well-known instance of two U.S. Marines from Michigan who were tattooed at the same time in Melbourne during World War II; both developed tuberculoid lesions in the tattooed areas two and a half years later.

As indirect evidence of the skin route, Rogers and Muir ([22]) have noted that initial lesions were more frequent on the feet and legs of patients from stony regions of India than in patients from regions where the soil was alluvial. It is also well known that initial lesions are found more frequently in the extremities and buttocks than elsewhere in the body, i.e., exposed parts and favored sites of trauma, skin diseases, and insect bites. Khanolkar ([15]) holds that bacilli may even pass through intact skin and find their way anywhere under the epidermis through the superficial lymphatic network. *M. leprae* may have this ability, although it is doubtful if a bacterial agent can pass through unbroken skin.

The widespread and symmetric distribution of cutaneous lesions in lepromatous leprosy, the finding in lepromatous patients of enormous numbers of bacilli in almost all internal organs at autopsy, and the almost sudden appearance of multiple, widespread, bacteriologically positive lesions in reactional tuberculoid leprosy, are indicative of systemic dissemination, but do not exclude the skin as the point of entry. The studies by Lara and Nolasco ([16,20]) of early cutaneous lesions in Culion children led them to conclude that these were primary foci and not a result of dissemination. Newell ([19]), on the other hand, holds that infection through the nasopharynx could be in greater agreement with existing evidence than the percutaneous route, and that the

predominance of solitary or unilateral initial skin lesions can be attributed to trauma as a localizing factor.

Although not very much can be done at this time regarding the question of the portal of entry, which is still unsettled, field studies might be able to provide some evidence of an association between both frequency and location of initial lesions, and the occurrence of antecedent trauma or other skin conditions. A minor study, for example, could deal with possible differences in the location of primary lesions between males and females or among comparable groups varying only with respect to frequency of injuries to the skin.

RESISTANCE AND NATURAL REACTIVITY TO LEPROMIN

We are unable to explain such variations in resistance as the excess of the lepromatous disease in the male sex, the decline in attack rates after adolescence, or the development of the severe lepromatous form instead of the milder tuberculoid. Reactivity to lepromin has been interpreted to indicate resistance, sufficient at least to protect against infections of lepromatous type, because the Mitsuda reaction is negative in the lepromatous type and positive in the tuberculoid type and because, in some correlation with attack rates, reactivity to lepromin increases rapidly with age from complete negativity in infancy to almost universal positivity among adults ([10,11,19]). This interpretation may be correct, but still lacks the support of direct proof obtainable only by a good study of comparative attack rates in known lepromin-positives and lepromin-negatives, particularly among adults.

Most cases of lepromatous leprosy are tested and found lepromin-negative after the disease has become manifest. Previous reactivity, whether positive or negative, is not known. It is possible for such cases to have been lepromin-positive and to have lost reactivity upon developing the disease. The author has observed three instances of lepromatous leprosy in lepromin-positive persons who subsequently became lepromin-negative when the lepromatous lesions appeared. Added evidence that reactivity to lepromin may change in either direction is found in the now well known finding ([1]) that tuberculoid cases undergo weakening and even abolition of lepromin reactivity during exacerbations or reactions, and that this lessened or abolished reactivity reverts to its former positive state when the acute phase subsides. On the other hand, normal adults tend to remain permanently and often strongly reactive to lepromin apparently throughout life, just as most lepromatous cases tend to be persistently lepromin-negative for many years after achieving clinical and bacteriologic arrest.

As far as reactivity to lepromin can be taken as an indication of resistance, there seems to be no proof that males are any less resistant to leprosy than females, or contacts less resistant than noncontacts. The Cebu studies ([7, 10, 11]) failed to show any appreciable difference in reactivity between males and females of any age, or between contacts of lepromatous cases and noncontacts, the differences in attack rates between these groups notwithstanding. Studies by Chatterjee ([2]) and Cochrane ([3]) tended to show a lower reactivity among child contacts than among unexposed children, but the numbers tested were not large. Newell ([19]) states that, in any population, the maximum prevalence rate for lepromatous leprosy would always be lower than the total proportion of lepromin-negatives, and that an added factor of selection probably still existed within the Mitsuda-negative group. If such were the case, or if lepromatous disease were unrelated to prior lepromin reactivity, no differences would be expected in reactivity between males and females or among contacts and noncontacts. It is obvious that many questions on resistance and on the significance of reactivity to lepromin can be answered only by a careful long-term study of specific attack rates among known lepromin-positives and lepromin-negatives.

Questions arise also regarding the nature and causes of natural reactivity to lepromin. Our studies ([12]) up to the present suggest that the rapid acquirement of reactivity in childhood, as age increases, can not be entirely explained by infection with *M. leprae, M. tuberculosis* and even with

mycobacteria; i.e., reactivity is apparently gained even in the absence of any mycobacterial infection. Some unknown possibly environmental factor unrelated to mycobacterial infection appears to make children, at least in the Philippines, positive to lepromin very early in life. More field studies are needed to determine its nature, such as one on the reactivity of different groups of children comparable in sex and age but living in widely divergent environments. There are no published studies of comparative lepromin reactivity in children of endemic and nonendemic areas tested with the same lepromin and using the same criteria of positivity.

Doull [6] has considered the difficult problem of the role of nutrition in the disease. There is no available evidence at present that a dietary deficiency predisposes to leprosy, but it is a possibility to be considered, even if remote. Comparisons should be made, by those competent in such matters, of possible differences or deficiences of diet between areas of high prevalence and of low prevalence, preferably in the same geographic locality.

BCG VACCINATION AS A PROPHYLACTIC MEASURE

The value of BCG vaccination has long been a major point of discussion. It is generally accepted that BCG will induce lepromin reactivity in a large proportion of lepromin-negative children. Although children become rapidly reactive, with increasing age, from natural causes [10,19], it is thought that the accelerated reactivity induced by BCG is beneficial, as it might confer immunity during the period of greatest susceptibility, i.e., early childhood. The value of BCG vaccination remains unassessed, however, because none of the "trials" thus far reported can be said to be strictly controlled and unbiased. There is urgent need for an acceptable study of attack rates, both for lepromatous and nonlepromatous forms, in large groups of vaccinated and control children. The children should be of the youngest possible ages, preferably contacts; and the vaccinated and unvaccinated groups must be strictly comparable in all possible respects but that of BCG vaccination, including distribution as to sex and age, conditions of exposure, and prior and subsequent reactivities to lepromin and tuberculin. If the study is limited to children under three years of age at the outset, initial tuberculin reactivity need not be taken into account, as all the children may be presumed to be tuberculin-negative.

It is admittedly difficult to conduct an acceptable BCG trial, because of the many factors to be considered in addition to BCG vaccination, and on account of the long incubation period and low attack rates for lepromatous leprosy, even in exposed children. Large numbers would be required, as a change only in the lepromatous type may have to be the measurement of success. Nevertheless, the value of BCG can be determined only by field studies.

CHEMOPROPHYLAXIS

The use of sulfones as a prophylactic, especially for intimately exposed persons, particularly children, has long been recommended. Extensive experience with sulfone therapy may have largely dispelled any fear of possible toxicity in children. As with BCG trials, however, the value of chemoprophylaxis can be determined only by field studies of attack rates in treated and control children comparable in all respects except prophylactic sulfone therapy.

HEREDITARY PREDISPOSITION TO LEPROSY

Existing evidence has shown that children of leprous parents isolated at birth do not acquire the disease more frequently than others. The high attack rate in families with a lepromatous index case can be attributed as much to opportunities for exposure as to a possible inherited predisposition to the infection. There have been no studies of attack rates in persons directly related to the primary or index case in the household as compared to those in persons not related, but equally exposed, to the index case.

The advocates of Rotberg's anergic "N-factor" hypothesis believe that some persons are constitutionally incapable of ever becoming lepromin-positive at any age and

on any provocation, whether by BCG or repeated lepromin testing, and that these persons are the ones liable to contract lepromatous leprosy. It is reasonable to expect that heredity would play a significant part in the possible existence of such persons. Field studies should be made to verify Rotberg's "anergic" hypothesis. Lepromin reactivity in general should also be studied on a genetic basis.

The occurrence, clinical type and course of leprosy in identical twins, as compared to nonidentical twins, should be studied as a means of establishing a possible hereditary factor in leprosy. The author has observed instances of concurrent leprosy in four pairs of identical twins and in only one member of a pair of nonidentical twins. In three pairs of identical twins, the disease in each pair was lepromatous and remarkably alike in course. In the fourth pair, female children six years of age, the lesions were of early lepromatous appearance and histopathology, with numerous bacilli, in one, and of still indeterminate type, with few bacilli, in the other. The nonidentical pair were adolescents of opposite sexes; the male twin had a large, bacteriologically positive, anesthetic lesion of indeterminate histopathology, while the female was healthy at last examination. Efforts should be made to uncover all possible instances of the disease in identical and nonidentical twins, as there is a strong indication that the existence of a hereditary predisposing factor may be shown in this manner.

The possible occurrence of a familial tendency toward either tuberculoid or lepromatous leprosy might also be a means of establishing a hereditary factor; field studies should be made of the frequency of secondary cases of either type in large numbers of families, in some relation to the type of leprosy in the index cases.

NEED FOR MORE CLINICAL AND LABORATORY RESEARCH IN THE FIELD

The confusion and disagreements in the clinical aspects of leprosy are undoubtedly due in part to its great complexity and variation as a disease, but they are attributable also to a lack of long and continued observations of its clinical course, especially in cases seen in the field and seldom in leprosaria. The course and development of all forms of leprosy, from earliest recognition to maximum development or arrest, can be learned only by painstaking clinical, histopathologic and immunologic examinations repeated at frequent intervals over many years. Such important questions as the significance and prognosis of minimal lesions, especially in children, the origin of borderline leprosy, the frequency of changes in type or in reactivity to lepromin, and the frequency of relapses or of reactional episodes, are answerable only by such studies, most of which must be done in the field. Although these are clinical changes, the frequency of their occurrence is of obvious epidemiologic significance.

Another important question answerable only by controlled field studies is that of the extent to which sulfone therapy can prevent or limit peripheral nerve damage and resulting deformity, especially in tuberculoid cases. A more basic question could be that of the value of instituting sulfone therapy in cases with nonlepromatous lesions of minimal extent, which have been shown to be largely self-healing, and furthermore, noninfectious. In highly endemic areas where personnel is lacking, it would be practical to limit mass treatment only to cases that are likely to progress.

PREVALENCE SURVEYS

The importance and continuing need of obtaining reliable estimates of the prevalence of the various types of leprosy must be stressed. Only by reliable prevalence rates can an adequate basis be provided for the direction of control measures and for the measurement of results. It is not possible to examine entire populations, and reliance must be placed on sampling surveys, the fundamentals being to determine the method of selection and numbers of persons to be examined. Joint planning by leprologists, epidemiologists and statisticians is necessary. Because of the scarcity of qualified personnel, the WHO and similar organizations should continue to make experts available for the planning of such sampling surveys. A fact that makes esti-

mations of prevalence difficult is the uneven and extremely focal distribution of leprosy all over the world.

SUMMARY

Leprosy problems requiring further field research are discussed in the hope that they may be studied by the WHO and other organizations with the necessary personnel and facilities. To further assess the role of the various clinical types in the spread of the disease, studies should be made of the relative frequency with which leprosy in young children can be traced to contact with lepromatous, tuberculoid or "missed" cases, respectively. The frequency and nature of reactions in tuberculoid leprosy should be studied in different geographic areas. The possible existence of subclinical or symptomless infections should be verified. The role of arthropods in the transmission of leprosy should also be further investigated.

The true relationship of lepromin reactivity to resistance can be ascertained only by more field studies of attack rates in large groups of known lepromin-positive and lepromin-negative persons, especially in the adult population. The values of BCG vaccination and chemoprophylaxis remain unassessed, and they also can be determined only by field studies of type-specific attack rates in large numbers of vaccinated (or treated) and control children, comparable in all respects except that of BCG or chemoprophylactic therapy, respectively. The difficulty of undertaking such studies is stressed.

To verify hereditary predisposition to the disease, more studies should be made of the occurrence, type and course of leprosy in identical, as compared with nonidentical twins; of a possible familial tendency toward either the lepromatous or the tuberculoid forms; and of lepromin reactivity in general on a genetic basis.

The need is stressed for more detailed and prolonged clinical and laboratory studies of the course and development of all the types of leprosy, especially those seen in the field. Finally, the importance and continuing need of obtaining reliable estimates of prevalence are emphasized.

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Dr. Sartwell. I wish to express our gratitude to Dr. Guinto for a very scholarly presentation, the nature of which does not preclude discussion, but time, unfortunately does not permit it now.

The next paper will be presented by Dr. Baruch S. Blumberg, Associate Director for Clinical Research at the Institute for Cancer Research in Philadelphia. His topic is "Leprosy research through genetics."